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EFFECT OF COHERENCE TIME OF THE APPLIED MAGNETIC FIELD ON ORNITHINE DECARBOXYLASE ACTIVITY

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Skepticism over the possibility of weak electromagnetic fields affecting cell function exists because endogenous thermal noise fields are larger than those reported to cause effects. Four-hour exposure to a 55- or 65-Hz field approximately doubles the specific activity of ornithine decarboxylase (ODC) in L929 cells. To test the idea that the cell discriminates against this thermal noise because it is incoherent, partial incoherence was introduced into the applied field by shifting the frequency between 55- to 65-Hz at intervals of τ_{coh} - $\delta\tau$ where τ_{coh} is a predetermined time interval and $\delta\tau << \tau_{coh}$ varies randomly from one frequency shift to the next. To obtain the full ODC enhancement, coherence of the impressed signal must be maintained for a minimum of about 10s. For τ_{coh} = 5.0s a partial enhancement is elicited, and at 1.0s there is no response. Unfortunately coherence times of this duration are too short to solve the thermal noise puzzle.

Concern over possible adverse health effects resulting from exposure to electromagnetic fields (EMF) has generated an increasing effort to determine how fields interact with biological systems. Results from cell culture studies have documented alterations in cell metabolism after exposures to extremely low frequency fields (1). Such data make it clear that EM fields interact with cells and affect their metabolism, but, neither the mechanisms of the interaction nor the long term biological consequences of such responses are understood. Many of the reported EMF effects have been obtained with applied time varying magnetic fields as low as 1 μT with associated induced electric fields below 1 μV/cm. The magnitudes of such fields are well below the random thermal noise fields generated by the thermal motion of ions in and about the cell (2)(3). It is, thus, a mystery as to how cells can detect, and respond to them.

Because an important characteristic of thermal noise fields is their incoherence, we have explored the possibility that the cell's signal transduction mechanism might demand a certain degree of coherence in the applied fields before it would respond to them. In this way the thermal field would be ignored by the cell. We have explored this concept experimentally by asking whether, during exposure, a time varying EMF must maintain coherency over some

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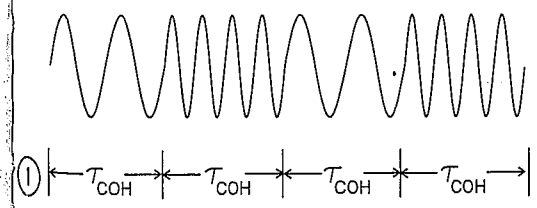
minimum interval to elicit a cellular response. The coherence time is loosely defined as the time interval over which we can reasonably predict the frequency, phase, and amplitude of the field. The biological endpoint selected for this purpose was the EMF-induced enhancement of specific activity for the enzyme ornithine decarboxylase (ODC) in murine L929 fibroblasts. The effect of the signal coherence time was examined for 60 Hz magnetic fields.

METHODS

Logarithmically growing cultures of murine L929 cells, maintained in Eagle's minimum essential medium with 5% fetal bovine serum, were plated 24 hr prior to magnetic field exposure. To avoid serum stimulation of ODC activity, the culture medium was not changed before experiments were begun. ELF exposures were conducted using incubator-housed Helmholz coils to produce sinusoidal, 60 Hz horizontal magnetic fields of 1 to 100 μT. Four 25 cm^2 flasks of cells were used for each exposure and to serve as controls four identical flasks were placed in an incubator chamber adjacent to that housing the Helmholz coils. At the end of exposure cells were harvested by gentle scraping, washed with phosphate buffered saline and stored as frozen pellets. Ornithine decarboxylase activities were assayed by the procedure of Seely and Pegg (4) modified by addition of 0.2% Nonidet P-40, 50 μg/ml leupeptin, and 50 μM pyridoxal-5-phosphate to the cell lysis buffer. Results of each set of experiments are expressed as the mean ratio of the enzyme activities of exposed cultures to those of the corresponding controls (± SEM).

A computer program which interfaced with a function generator was used to determine the ELF frequency and also the time interval for which a given frequency was maintained. At user-selected intervals (henceforth termed coherence times, or τ_{coh}) the frequency of the ELF field signal was alternately shifted from 55 Hz to 65 Hz (see Figure 1). Coherence times of the exogenous fields were varied from 0.1 to 50 s. The phase of successive intervals was randomized by inserting a small uncertainty in τ_{coh}. Thus the time between frequency shifts was actually τ_{coh} - δt where $\delta t << \tau_{coh}$ and is a random time which varied between 0 and 0.05 s.



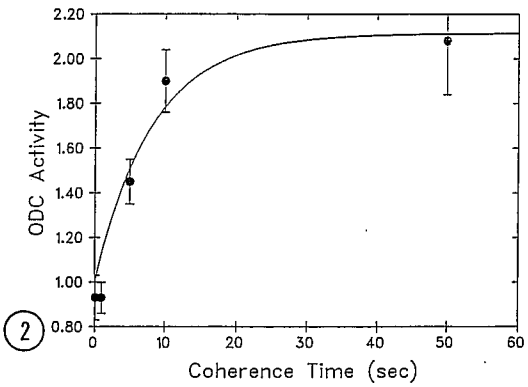


Figure 1. A plot demonstrating the partially coherent waveform created by shifting frequencies from 55- to 65- Hz at intervals of time, $\tau_{coh} \pm \delta\tau$, where $\delta\tau$ is a random number ($<< \tau_{coh}$) varying between 0 and .05 s.

Figure 2. Plot of the enhancement of ODC activity (exposed/control) as a function of the coherencetime, τ_{coh}, of the applied field. The solid line is the best fit to the mathematical function given by Eq. 1 where τ_{cell} is found to be 8.2 s. The experimental points shown represent a minimum of six different exposures.

RESULTS AND DISCUSSION

Cultures were subjected to a series of exposures to 60 Hz magnetic fields of 1, 10 or 100 μT, for times ranging from 1 to 8 hr. The enhancement of ODC activity was measured in terms of the ratio of exposed/control activity. Maximal enhancement of ODC activity (2.04 ± 0.21) was produced by 4 hr exposure to a magnetic field of 10 μT. The associated induced electric field was approximately .04 μV/cm. Comparable enhancements of ODC activity (1.79 ± 0.20, 2.10 ± 0.35) were obtained with frequencies of either 55 or 65 Hz. Using 4 hour exposures, 10 μT fields, and frequencies shifting alternately between 55- and 65-Hz, we varied the coherence times from 0.1 to 50.0 s.

The results are plotted in Figure 2. They show that application of fields for four hours but with coherence times of 10 or 50 s did produce enhancements in ODC activities. The amount of enhancement was (within experimental accuracy) the same as that observed after exposures which were coherent for the full four hours of exposure. In contrast, for coherence times of 0.1 or 1.0 s no enhancement of ODC activity was observed. A 5 s coherence time produced a level of enhancement (1.54 ± 0.06) that was intermediate between control values and those obtained with τ_{coh} of 10 s or longer.

The ratio of exposed/control ODC activity, [ODC], plotted in Figure 2 was fit to the function,

$$[ODC] = 1 + 1.26\left(1 - e^{-\frac{\tau_{coh}}{\tau_{cell}}}\right) \qquad (1)$$

with best fit value of τ_{cell} = 8.2 ± 3 s. Thus there appears to be some fundamental time constant, τ_{cell} associated with the cell signal transduction mechanism. For the cell to respond to an ELF signal it is necessary for the exogenous field to maintain coherence for a minimum time interval greater than about several seconds, with full response requiring an interval greater than about 10.0 s. Some sort of signal averaging thus appears to function in producing field-induced enhancement of ODC activity by L929 cells.

We now consider whether this coherence phenomenon will be sufficient to account for the ability of cells to discriminate against the thermal noise caused by thermal fluctuations in the position of nearby ions. To determine the thermal electrical field noise we use the Johnson-Nyquist expression where the time average noise voltage V_{kT} and electric field E_{kT} are expressed as,

$$\overline{V_{kT}^2} = \frac{4\rho kT\Delta\nu}{d} \;;\; where\; E_{kT} = \frac{\sqrt{\overline{V_{kT}^2}}}{d} \qquad (2)$$

In these expressions ρ is the resistivity of tissue, Δν is the band width of the cell signal transduction mechanism, d is the diameter of the cell, k is the Boltzmann constant, and T is the

absolute temperature. Following Adair ( ) we use these expressions assuming that d = 20 μm, ρ = 2 Ω·m, and $\Delta\nu$ = 100 Hz. This predicts that $E_{kT} \approx .02$ V/m. Thus we find that the thermal noise field is about 5,000 times larger than the magnitude of the 60 Hz electric fields induced in this experiment.

How does the requirement of a minimum value of τ_{coh} affect the signal-to-noise calculation? Weaver and Astumian (2) have suggested that if signal averaging is present the minimum detectable field would be given by the expression,

$$E_{min} = \frac{E_{kT}}{\sqrt{\nu \tau_{avg}}} \qquad (3)$$

where ν is the frequency of the applied signal and τ_{avg} is the time over which the cell averages the signal. If we assume that that $\tau_{avg} \approx \tau_{cell}$ the minimum detectable field is still over 100 times larger than the applied fields used in this experiment. In fact, to obtain an improvement in signal-to-noise of 10,000, the averaging process would have to last for about 10^6 seconds (i.e. > 100 hours) which is clearly an unreasonable averaging requirement.

Even though our results do not explain the signal-to-noise puzzle, the necessity for a minimum coherence time will have to be accounted for in any model proposed for the mechanism by which cells detect an applied EM field. In addition to EMF frequency and time of exposure, coherence time must be considered an important factor in determining the cellular response.

ODC is a critical enzyme, required for DNA replication and cell proliferation, and so modification of its enhancement by an applied field is of general interest for questions of EMF exposure. We suggest, however, that the coherence phenomenon noted in these experiments is likely of more widespread consequence, and that other biological responses with demonstrated EMF sensitivity will display comparable coherence dependence. Indeed a similar effect has been observed in studies of EM induced abnormalities in chick embryos (5).

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